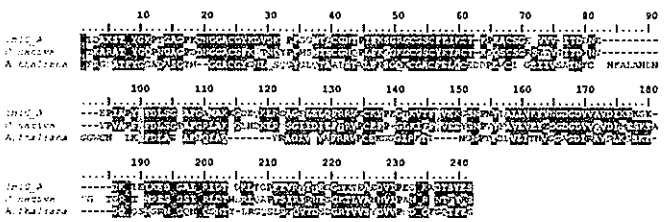
LETTERS

Letters to the Editor

Letters (~300 words) discuss material published in *Science* in the previous 6 months or issues of general interest. They can be submitted by e-mail (science_letters@aaas.org), the Web (www.letter2science.org), or regular mail (1200 New York Ave., NW, Washington, DC 20005, USA). Letters are not acknowledged upon receipt, nor are authors generally consulted before publication. Whether published in full or in part, letters are subject to editing for clarity and space.

How Unique Is the Rice Transcriptome?

IN THE REPORT "COLLECTION, MAPPING, AND annotation of over 28,000 cDNA clones from *japonica* rice" (S. Kikuchi *et al.*, 18 July, p. 376), the Rice Full-Length cDNA Project Team provides a detailed description of the rice transcriptome. The authors claim that 36% of the tested rice transcripts are not homologous to the *Arabidopsis thaliana* transcriptome. The authors also suggest that more than 100 InterPro domains (*1*) can be found in *Oryza sativa japonica*, but not in *A. thaliana*. Does this mean they are absent from the *Arabidopsis* genome? In many cases, even the most sophisticated bioinformatics methods can fail to detect evolutionary relationships between protein families that can be confirmed by functional and structural similarity. To validate these claims, we conducted an analysis of the reported results.



Alignment of *O. sativa japonica* (GenBank accession number AK101357) and *A. thaliana* (GenBank accession number NP_196148.1) *major pollen allergen Lol pI* proteins with a Major Timothy Grass Pollen Allergen (1n10_A). The sequence similarity of these proteins was proved with the 3D-Jury system (scores > 100) (*8*).

Using a combination of profile-sequence searches (*2*, *3*), we found *A. thaliana* homologs for 33 out of the 100 rice transcripts annotated by the Consortium as containing rice-specific InterPro domains (*1*). For example, homologs of the *major pollen allergen Lol pI*, claimed to be rice-specific, were found in several copies in the *A. thaliana* transcriptome (see figure). While investigating the original results, we found that in many cases, one of the methods used [e.g., HMM-Pfam (*4*) and BlastProDom (*5*)] failed to match the corresponding genes from both genomes (*3*), a potential source of the problem.

Ten additional rice-specific InterPro annotations comprise very short, statistically insignificant motifs and hits. For example, Prosite (*6*) locates a 7–amino acid "Bombesin-like peptide" (InterPro: IPR000874) in sequence AK072501 (KOME accession number 208521), but fails in 24 *A. thaliana* and 5 *japonic* rice orthologs (*3*).

In our investigation, we concluded that over 40% of the 100 rice-specific domain assignments are not justified. Using more sophisticated sequence similarity search tools, such as profile-profile comparison methods (*7*), would probably decrease the number of potentially rice-specific InterPro domain assignments to below 50. Even then, the true number is a function of the InterPro database size, the particular time of the analysis, and the type of applied bioinformatics methods. The comparison of functional capabilities of two transcriptomes remains a difficult task given the current accuracy of computational approaches.

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Response

WYRWICZ *ET AL.* SUGGEST THAT THE FL-cDNA clones we described as rice-specific in our Report can be found in the *Arabidopsis thaliana* genome using different methods. We analyzed the sequence of rice full-length cDNA clones with the InterPro Database in the middle of 2002 and submitted our manuscript in December 2002. We had reviewed several published papers and found that the best way to make the comparison of rice FL-cDNA clones and *Arabidopsis* clones was to use the InterPro domain search. At that time, we did not have the opportunity to access the method recommended by Wyrwicz *et al.* Many months have passed since the submission and review process. During this interval, many databases were updated, and many research tools were developed. Thus, the results in our Report are not current. Genome data are developing every day. This comment is very helpful for our future work, and we are willing to use the method that Wyrwicz *et al.* recommend.

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Another Grand Challenge: Mental Health

WE WERE DISAPPOINTED TO FIND THAT NONE of the "Grand Challenges in Global Health" identified by H. Varmus *et al.* (Policy Forum, 17 Oct., p. 398) addressed mental health problems, particularly those arising from exposure to traumatic events such as war and disaster. Rates of psychiatric disorders, including major depression, substance abuse, and posttraumatic stress disorder (PTSD), are markedly elevated among trauma-exposed individuals. For example, although the life-time prevalence of PTSD in the United States is 7.8% (*1*), rates of 37.4% in Algeria, 28.4% in Cambodia, 15.8% in Ethiopia, and 17.8% in Gaza (*2*) illustrate how PTSD disproportionately affects the developing world.

> **"There is a pressing need to treat the consequences of exposure to traumatic events in developing nations."**
>
> –SCHNURR ET AL.

Many traumatic events that occur in developing nations are nondiscriminating with regard to age and gender, potentially affecting all living generations. In addition,

the impact of trauma often reverberates through succeeding generations because the events themselves and the disability they cause undermine the social fabric and disrupt key institutions that are essential for public health and societal progress. Given the strong biological and biomedical slant of the Grand Challenges, it is worth noting that the negative impact of traumatic stress extends to basic issues of physical health as well.

There is a pressing need to treat the consequences of exposure to traumatic events in developing nations. However, most treatment research has been conducted in countries that have substantial public and private mental health resources. It is time to address this vacuum by generating an empirical base of culturally relevant and sustainable interventions for countries that have limited mental health infrastructure. Effective intervention can ameliorate the adverse mental, physical, and social consequences of traumatic exposure among the most vulnerable populations in our global society.

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†The views expressed are those of the authors and do not necessarily represent the official policy or position of the National Center for PTSD, the Department of Veterans Affairs, or the U.S. government.

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The Grand Challenge of Birth Control

I READ WITH GREAT INTEREST THE LIST OF 14 "Grand Challenges in Global Health" (H. Varmus *et al.*, Policy Forum, 17 Oct., p. 398) and wish to add a 15th: to develop a method of birth-rate reduction to offset the population increases brought about by Grand Challenges 1 through 14.

It is foolhardy to believe that human welfare is improved in the face of a successful Grand Challenge death rate reduction without establishing a working program for this 15th challenge. In fact, it is necessary to have it in place before the effects of the other Grand Challenges occur. Political and bureaucratic excuses abound when it comes time to implement a timely and effective birth-control program. Without such a program, the newly spared populations will move to the nearest urban slums to die too soon of some other malady, one not the focus of the Grand Challenge program.

It is incumbent upon those who have the intelligence and skills to reduce the deaths caused by infectious disease to take the responsibility to not make matters worse when their goals are being achieved. I now suggest that Bill Gates and NIH take such full responsibility for their spending plans.

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The Effects of Manganese in Air

JOCELYN KAISER'S ARTICLE "MANGANESE: A high-octane dispute" (Special Issue on Metals: Impacts on Health and the Environment: News, 9 May, p. 926) discusses a study of a Canadian population by Donna Mergler and colleagues (*1*, *2*) that found associations between manganese blood levels and performance on motor and memory tests. Because Mn blood concentrations in this study were within normal levels (*3*–*5*), which primarily reflect consumption of whole grains, cereals, and tea (*6*, *7*), Mergler's study suggests that normal variations in blood manganese, due to diet, are associated with subtle neurological changes.

Although Kaiser's article implied that the association with blood Mn found by Mergler was due to Mn in air, the design of the study was inadequate to address this question. Air sampling was limited to four fixed locations and was conducted several months after the blood samples were collected. "Downwind" was defined in relation to the site of a former Mn plant, which had been closed for 5 years [although about one-half of the "downwind" area was actually upwind of the plant (*2*)]. There is no evidence that air Mn at the time of the study was related to this plant.

In a large personal sampling study recently conducted in Toronto (*8*), the median personal exposure to Mn in PM_{10} (particles with a mean aerodynamic diameter less than or equal to 10 μm) was 0.015 $\mu g/m^3$, which was also the average level in fixed samples in the Mergler study. Based on the recommended dietary intake of Mn

(*7*), and fractional intake of Mn from the gut and lungs (*9*, *10*), 0.015 μg/m³ Mn in air would contribute less than 0.1% of Mn in blood (*11*). This is consistent with occupational Mn studies (*12*–*14*), which predict that 0.015 μg/m³ Mn in air would contribute only 0.002 to 0.03% of Mn in blood (*15*). Thus, it is unlikely that air Mn made a meaningful contribution to blood Mn in this study, and consequently, it is unlikely that air Mn was responsible for the associations found by Mergler between blood Mn and neurological outcomes.

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5. For blood Mn concentrations among normal populations, (*3*) indicates a mean of 9 μg/liter and a (95%) range of 4 to 20 μg/liter and (*4*) indicates a median of 13.6 μg/liter, and a range of 8 to 19 μg/liter, whereas in Mergler's study, the mean was 7.5 μg/liter with a range of 2.5 to 16 μg/liter.
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11. Assuming the recommended dietary intake of 3.5 mg Mn per day (*7*), of which 3 to 7% is absorbed (*9*), predicts at least 100 μg/day absorbed from dietary sources. Assuming 30% of inhaled Mn is absorbed (*10*), a breathing rate of 20 m³/day and 0.015 μg/m³ Mn in air predicts that only 0.1 μg/day Mn from inhalation is absorbed.
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15. Applying the increase in Mn in blood per μg/m³ respirable Mn [using a factor of (10/20) × (5/7) to convert from occupational to continuous exposure] from occupational studies (*12*–*14*) results in predicted contributions to blood Mn from 0.015 μg/m³ Mn in air of 0.002% (*12*), 0.01% (*13*), and 0.03% (*14*) of the blood levels in unexposed controls.

Response

WE WOULD LIKE TO CLARIFY SOME OF THE issues raised by Crump and Clewell. As they point out, the Mergler *et al.* (*1*) study shows an inverse association between blood Mn levels and performance on certain motor and memory tests, consistent with knowledge of the effects of Mn in the brain. A geographic algorithm, applied to the blood Mn data, distinguished two significantly distinct areas, with higher levels in an urban area, which was also downwind from a former ferro- and silico-manganese alloy production plant (*2*). Although air measurements were limited to 24-hour high-volume sampling for total particulate matter (TP) and PM_{10} at four sites, during three consecutive days at each site over a 3-week period, results showed that the urban site and the site 3 km from the plant had similar Mn concentrations, higher than those measured at the sites upwind and south of the plant (approximately three times higher for Mn TP and twice as high for Mn PM_{10}).

Given these data, we created a surrogate geographic variable for airborne Mn, based on postal code, with respect to the former plant location (upwind/downwind) and classified persons accordingly. It should be noted that only 12 individuals (4% of the total study group) lived in the postal code area that Crump mentions, half of which was upwind of the plant. For this classification, the actual location of each person was verified and nine lived very near the sampling site in this postal code, while three lived a short distance away.

We explored the possible contribution of different media (air, water, and diet) to blood Mn concentrations. The results showed that living in the area "downwind" of the plant, as defined by the geographic variable, and estimated Mn dietary intake from cereals and green vegetables were both significantly associated with blood Mn, taking into account age, gender differences, and the contribution of serum iron.

In the discussion section of the article by Baldwin *et al.* (*2*), we suggested that the point source from the former plant, together with traffic density, could contribute to the observed distribution of blood Mn and we stated that "this interpretation is tentative, since few air measurements were taken." We also recommended that "the contributions of airborne Mn to blood Mn levels in other communities living close to potential sources of manganese pollution should be further explored..." It is unfortunate that the Toronto study (*3*), cited by Crump and Clewell, where extensive measurements were made of airborne Mn, did not examine the relation between airborne and blood Mn.

Jocelyn Kaiser's article brought out many of the issues underlying the debate over the health effects of increasing Mn levels. Many uncertainties remain in our understanding of environmental Mn and its effects on human populations. Clearly, we need more concerted efforts to carry out comprehensive studies on possible exposure sources and health effects, particularly for populations potentially at risk, such as children and the elderly.

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CORRECTIONS AND CLARIFICATIONS

Viewpoint: "Insulin signaling in health and disease" by M. F. White (5 Dec., p. 1710). In the abstract and reference (*4*), the link pointing to the connections map published in STKE should end with capital letters. The correct URL is http://stke.sciencemag.org/cgi/cm/CMP_12069.

Reports: "Oceanic Rossby waves acting as a 'hay rake' for ecosystem floating by-products" by Y. Dandonneau *et al.* (28 Nov., p. 1548). There were errors in three of the figures. The ranges indicated in Fig. 1A and Fig. 2A should read "+2.5e–8" to "–2.5e–8," and the range indicated on the *x* axis in Fig. 4 should read "–3.00E–08" to "3.00E–08."

Books *et al.*, Nota Bene: "Spellbound" by O. Smith (28 Nov., p. 1508). The curators of the National Library of Medicine's exhibition *Changing the Face of Medicine* are Ellen S. More and Manon Parry.

Reports: "Control of effector CD8$^+$ T cell function by the transcription factor *Eomesodermin*" by E. L. Pearce *et al.* (7 Nov., p. 1041). On p. 1043, in the third paragraph of the middle column, superscript symbols were removed, which changed the meaning of three sentences. The correct sentences are as follows: "Splenocytes from littermate *Eomes*$^{+/+}$ and *Eomes*$^{+/-}$ mice (*21*) were stimulated via the TCR for 3 days. Cells from *Eomes*$^{+/-}$ mice indeed exhibited reduction in Eomes mRNA (Fig. 2E), and this partial knockdown of Eomes levels was accompanied by a substantial reduction in perforin mRNA (Fig. 2E)... We detected only minimal loss of IFN-γ expression in CD8$^+$ T cells from *Eomes*$^{+/-}$ mice, possibly owing to the partial knockdown and redundancy from the actions of T-bet (*15*)."

Special Issue on Brain Disease: Reviews: "Immunotherapeutic approaches to Alzheimer's disease" by A. Monsonego and H. L. Weiner (31 Oct., p. 834). In the fifth sentence of column two on page 836, the references cited are incorrect. They should read "(*45–48*)." Also, in the third sentence of column three on the same page, the references cited are incorrect. They should read "(*49–52*)."

News of the Week: "U.S. biodefense boom: Eight new study centers" by D. Malakoff (12 Sept., p. 1450). The map accompanying the article erroneously identifies the University of Maryland College Park as a winning institution in region III. That distinction belongs to the University of Maryland School of Medicine in Baltimore, MD, awarded a grant to lead the Mid-Atlantic Regional Center of Excellence in Biodefense and Emerging Infectious Diseases Research.

Special Section on Catalysis: News: "Water splitting goes au naturel" by J. Alper (14 Mar., p. 1686). The report of work done in 1999 by Kimberly A. Bagley in her lab at Buffalo State College, New York, to prove that carbon monoxide and cyanide were essential components in hydrogenases, was incorrect. The assignment of these ligands at the active site of NiFe hydrogenases was based on research that occurred at the University of Amsterdam in collaboration with Simon P. J. Albracht and co-workers of Swammerdam Institute for Life Sciences, Biochemistry, University of Amsterdam.

TECHNICAL COMMENT ABSTRACTS

COMMENT ON "Molecular Phylogenies Link Rates of Evolution and Speciation" (I)

Christopher C. Witt and Robb T. Brumfield

The association between rates of speciation and molecular evolution reported by Webster *et al.* (Brevia, 25 July 2003, p. 478) reflected a potentially insufficient correction for the node density artifact. Their 56 phylogenies were not independent and were sparsely sampled, which may have led to inaccurate estimates of relative speciation rate.

Full text at www.sciencemag.org/cgi/content/full/303/5655/173b

COMMENT ON "Molecular Phylogenies Link Rates of Evolution and Speciation" (II)

Andrew V. Z. Brower

Webster *et al.* (Brevia, 25 July 2003, p. 478) compiled published data to demonstrate a correlation between number of speciation events and rate of evolution. Some of these data sets did not include DNA sequences, and others did not compare relationships among species. In my view, these and other methodological problems may cast doubt upon their findings and conclusions.

Full text at www.sciencemag.org/cgi/content/full/303/5655/173c

RESPONSE TO COMMENTS ON "Molecular Phylogenies Link Rates of Evolution and Speciation"

Andrea J. Webster, Robert Payne, Mark Pagel

We showed that rates of speciation are significantly linked to rates of genetic evolution in 30 to 50% of phylogenetic trees across a range of taxa. Our methodology removed trees in which the node density artifact or biased taxon sampling might have affected results. Suggestions that these controls are insufficient or inaccurate misunderstand the derivation of our statistical model. Whether different taxa exhibit the effect to different degrees is an important topic for future studies.

Full text at www.sciencemag.org/cgi/content/full/303/5655/173d